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Nonalcoholic Fatty Liver Disease as an Emerging Risk Factor and Potential Intervention Target for Atherosclerotic Cardiovascular Diseases

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Abstract: Nonalcoholic fatty liver disease (NAFLD) is an underappreciated independent risk factor for atherosclerotic cardiovascular diseases (ASCVDs). In recent years, the risk of ASCVD has increased along with the prevalence of NAFLD. ASCVD events are highly prevalent and are the main contributor to death in patients with NAFLD. The association between NAFLD and ASCVD has been validated in numerous observational, cohort, and genetic studies. Most of these studies agree that NAFLD significantly increases the risk of developing atherosclerosis and ASCVD. In addition, the underlying proatherosclerotic mechanisms of NAFLD have been gradually revealed; both disorders share several common pathophysiologic mechanisms including insulin resistance, whereas systemic inflammation and dyslipidemia driven by NAFLD directly promote atherosclerosis. Recently, NAFLD, as an emerging risk enhancer for ASCVD, has attracted attention as a potential treatment target for ASCVD. This brief review aims to illustrate the potential mechanistic insights, present recent clinically relevant investigations, and further explore the emerging therapies such as novel antidiabetic and lipid-lowering agents that could improve NAFLD and reduce ASCVD risk.

Key Words: nonalcoholic fatty liver disease, lipid-lowering agents, antidiabetic agents, atherosclerotic cardiovascular disease, insulin resistance

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INTRODUCTION

Over the past decades, nonalcoholic fatty liver disease (NAFLD) has become a common dysmetabolic syndrome globally, with increasing prevalence in Asia.[1,2] The definition of NAFLD in most guidelines regardless of region is the accumulation of excess fat in the liver that is not because of heavy alcohol use.[2–4] NAFLD can be further subclassified into nonalcoholic fatty liver and nonalcoholic steatohepatitis (NASH); the latter includes fibrosis, cirrhosis, and hepatocellular carcinoma.[4] Our present understanding of NAFLD has expanded from being a hepatic manifestation of metabolic syndrome (MetS) to promoting atherosclerotic process, eventually leading to atherosclerotic cardiovascular diseases (ASCVDs) including coronary artery disease (CAD), ischemic stroke (IS), and other cardiovascular events.[2–5] Whether NAFLD is independently related to ASCVD remains debatable. However, in recent years, there has been increasing epidemiologic, genetic, mechanistic, and observational evidence to support that NAFLD can directly or indirectly aggravate the pathogenesis of atherosclerosis and related clinical events, indicating that NAFLD could be an emerging independent risk factor and potential therapeutic target for ASCVD. Most recently, the American Heart Association released a scientific statement to highlight the clinical implication of treating and preventing NAFLD to reduce the risk of ASCVD.[5] This narrative review systematically summarizes the relationship between NAFLD and ASCVD by discussing the underlying pathophysiologic mechanisms linking NAFLD to atherosclerosis and exploring the prospect of novel treatment strategies for NAFLD that could also benefit the risk reduction of ASCVD.

THE CLINICAL IMPLICATIONS OF NAFLD ON ASCVD

There is a large body of evidence on the relationship between NAFLD, subclinical atherosclerosis, and more advanced atherosclerotic events presented in Table 1.[6–21]

By measuring calcification, carotid intima-media thickness (C-IMT), and stiffness of the aorta, these studies tease out whether NAFLD is an independent risk factor that could predict the development of ASCVD.[9–16] Several of these studies assessed coronary artery calcification (CAC), which is a well-established surrogate marker for atherosclerosis burden in patients with NAFLD.[9–15] Individuals with NAFLD

seemed to be associated with CAC progression even after adjusting for confounders and metabolic risk factors. In a recent meta-analysis involving 10,060 participants, NAFLD patients significantly increased the risk of subclinical atherosclerosis in CAC progression (odds ratio [OR] 1.50, 95% confidence interval [CI], 1.34–1.68; $P = 0.001$),[22] suggesting NAFLD to be an independent risk factor for CAC progression. A community-based Kailuan prospective study among Chinese adults revealed that NAFLD was independently associated with elevated C-IMT after adjusting the conventional cardiovascular risk factors (OR 1.663, 95% CI, 1.391–1.989, $P < 0.0001$).[16] Interestingly, NAFLD is a risk factor for subclinical atherosclerosis regardless of ethnicity, as 1 recent meta-analysis of 172,385 subjects in 64 studies showed.[23] Taken together, these studies demonstrated that individuals with NAFLD have a stronger association with subclinical atherosclerosis as expressed by atherosclerotic plaque and noncalcified plaque, CAC score, and C-IMT than those without NAFLD. Most of them proved that this association is independent of traditional cardiovascular risk factors such as T2DM, hypertension, or dyslipidemia.

A growing number of studies have provided insights on the association of NAFLD with advanced atherosclerotic events such as CAD, MI, and IS.[6–8,17–21] Although the results of the study by Alexander et al biased toward the null,[17] many of these studies demonstrate the independent contribution of NAFLD to ASCVD after comprehensive adjustment of CVD risk factors. Therefore, NAFLD represents a risk enhancer for cardiovascular events. Nevertheless, prospective and long-term cohort studies with larger sample sizes are needed to testify the causality of NAFLD on ASCVD, which may help to risk-stratify individuals and guide treatment.

EPIDEMIOLOGIC EVIDENCE LINKING NAFLD WITH ASCVD

The global prevalence of NAFLD is estimated to be around 25%, and this number is slightly more in Asia at approximately 29%, with Indonesia at 51%, and the pooled prevalence in China close to 30%.[1] A recent study using a Markov model predicted that the prevalence of NAFLD will increase by 18%–29% in 8 countries (China, France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States) by 2030.[24] There have been numerous reports on the prevalence of NAFLD among patients with CVD. A population-based cohort study conducted in Minnesota, United States, with a mean follow-up of 7.6 years, reported that ischemic heart disease (IHD) made up 25% of deaths among patients with NAFLD, almost 2 times more than liver disease[25]; a larger national study of 55 million patients found that the presence of myocardial infarction (MI) in patients with NASH was 10.2%.[6] In another Finnish population-based cohort of 988 participants followed from 1991 to 2009, fatal and nonfatal coronary heart disease (CHD) was reported in 10.4% and 11.1% of those with severe fatty liver, respectively.[26] In a match cohort study of 22,048 patients from Germany, 12.8% of patients with NAFLD/NASH were diagnosed with CHD, and 2.9% were diagnosed with MI within 10 years, significantly higher than those without NAFLD/NASH.[7] A meta-analysis of 2,054,554 participants from 392 studies in China showed a significantly higher risk of CVD (OR 3.2, 95% CI, 2.27–4.50; $P < 0.001$) in patients with NAFLD.[27] In another meta-analysis of 16 observational prospective and retrospective studies involving 34,043 individuals with a median follow-up of 6.9 years, those with NAFLD were at 64% higher risk of developing fatal and nonfatal cardiovascular events.[28] Above all, the increasing epidemiologic data in different populations have revealed high incidence and severity of cardiovascular events among patients with NAFLD, suggesting that NAFLD may predict a future risk of ASCVD.

GENETICS CONTROVERSY OF NAFLD AND ASCVD

Common genetic variants may drive the manifestation of atherosclerosis in patients with NAFLD; well documented ones include *PNPLA3*, *TM6SF2*, and *GCKR*. Polymorphisms in the *PNPLA3* gene are known to confer a higher risk of hepatic fat accumulation and inflammation. In an Italian study, *PNPLA3* GG genotype was associated with greater severity of carotid atherosclerosis in younger patients with NAFLD[29]; conversely, a study in China showed that *PNPLA3* CC, but not GG genotype was associated with increased risk of subclinical atherosclerosis.[30] Dongiovanni and colleagues showed that patients with NASH who were carriers of *TM6SF2* E167K had lower serum lipid levels (triglycerides and total cholesterol), were more susceptible to liver damage, and had a higher risk of developing carotid plaques than noncarriers.[31] A study in the Han Chinese population also showed *PNPLA3* I148M and *TM6SF2* E167K variants may have a protective effect on CHD because of reduced serum triglyceride and low-density lipoprotein (LDL) levels.[32] Polymorphisms in the *GCKR* gene did not increase the risk of CAD in NAFLD Northern Han Chinese patients in a case–control study.[33] Carriers of *GCKR* risk alleles did not exhibit changes to serum fasting plasma glucose and triglyceride levels.[33] Likewise, in the IMPROVE study, *PNPLA3*, *TM6SF2*, and *GCKR* genetic variants were not associated with measures of subclinical atherosclerosis.[34] Moreover, in an exome-wide association study of plasma lipids in >300,000 individuals, *PNPLA3* p.Ile148Met and *TM6SF2* p.Glu167Lys variants were associated with lower blood triglycerides and LDL-C, lower risk of CAD, but higher liver fat.[35]

Mendelian randomization approach has also been used to investigate the causality of NAFLD and atherosclerosis. In a cohort study of the Danish population ($n = 94{,}708$; IHD: 10,897), Lauridsen et al found that the risk of IHD increased stepwise with increased liver fat content (OR 2.41, 95% CI, 1.28–4.51; $P = 0$ 0.004); the corresponding OR for IHD in individuals with and without NAFLD was 1.65 (95% CI, 1.34–2.04; $P = 3 \times 10^{-6}$).[36] There was also a stepwise increase in liver fat in subjects with *PNPLA3* I148M MM versus II genotype, with an OR of 2.03 (95% CI, 1.52–2.70; $P = 3 \times 10^{-7}$) for NAFLD. In contrast, this variant was not associated with the risk of IHD for MM versus II genotype (OR 0.95, 95% CI, 0.86–1.04; $P = 0.46$).[36] These results were in agreement with a meta-analysis of 279,013 subjects of whom 71,698 had IHD. In this study, the OR for IHD per M-allele versus I-allele was 0.98 (95% CI,

TABLE 1. Studies Exploring the Risk of Atherosclerosis in Patients With Nonalcoholic Fatty Liver Disease

Author, year	Geography	Study Type	Patient number, *n*	NAFLD Diagnosis	Impact of NAFLD on Atherosclerotic Outcomes after Adjustment for Risk Factors
Sinn et al, 2017[14]	Korea	Retrospective	4731	Ultrasound	Ratio of progression rates, 1.04 for CAC scores*
Cho et al, 2018[9]	Korea	Retrospective	1173	Ultrasound	Multivariate-adjusted OR, 1.53 for CAC progression 95†
Gummesson et al, 2018[10]	Sweden	Cross-sectional	1111	CT scan	Adjusted OR, 1.77 for CAC scores‡
Lee et al, 2018[13]	Korea	Cross-sectional	5121	Ultrasound	Adjusted OR, 1.18 for any atherosclerotic plaque§
					Adjusted OR, 1.27 for non-calcified plaque§
Zheng et al, 2018[16]	Mainland China	Cross-sectional	4112	Ultrasound	Adjusted OR, 1.663 for elevated C-IMT¶
					Adjusted OR, 1.068 for ba-PWV¶
Alexander et al, 2019[17]	Italy, Netherlands, Spain, and UK	Matched cohort	17.7 million	Not mentioned	Adjusted HR, 1.04 for stroke‖
Baratta et al, 2020[8]	Italy	Prospective	898	Ultrasound	Adjusted HR, 2.73 for cardiovascular events#
Ghoneim et al, 2020[6]	United States	Retrospective	55 million	Not mentioned	Adjusted OR, 1.5 for MI**
Koo et al, 2020[12]	United States	Retrospective	4185	CT scan	Adjusted OR, 1.38 for calcification in the thoracic aorta††
					Adjusted OR, 2.05 for calcification in the celiac trunk††
Kim et al, 2020[18]	Korea	Prospective	3,011,588	FLI	Adjusted HR, 1.98, 2.16, and 2.01 for cardiovascular death, non-fatal MI, and IS, respectively‡‡
Labenz et al, 2020[7]	Germany	Matched cohort	22,048	Not mentioned	Adjusted HR, 1.35 for CHD§§
					Adjusted HR, 1.34 for MI§§
Sinn et al, 2020[19]	Korea	Retrospective	111,492	Ultrasound	Adjusted HR, 2.14 for MI¶¶
Hsu et al, 2021[11]	Taiwan	Cross-sectional	1502	Ultrasound	Adjusted HR, 1.44 for coronary plaques‖‖
Tang et al, 2021[15]	Mainland China	Retrospective	418	CT scan	Significantly higher prevalence of non-calcified plaques ($P < 0.001$)
					Significantly higher rate of stenosis ($P < 0.001$)##
Xu et al, 2021[20]	Mainland China	Prospective	79,905	Ultrasound	Adjusted OR, 1.16 for IS***
					Adjusted OR, 1.27 for MI***
Zou et al, 2021[21]	United Kingdom	Retrospective	196,128	FLI	Adjusted HR, 1.01 for stroke†††
					Adjusted HR, 1.06 for CHD†††

*Adjusted for age, sex, smoking status, alcohol intake, body mass index, systolic blood pressure, total and high-density lipoprotein cholesterol, triglycerides, diabetes, use of antihypertensive medications, use of lipid-lowering drugs, hemoglobin A1c, and estimated glomerular filtration rate.

†Adjusted for age, sex, body mass index, smoking, drinking, exercise habits, coronary artery calcium score, follow-up interval, low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein.

‡Adjusted for sex, age, education, body mass index, alcohol, smoking, sedentary time, waist, physical activity, other metabolic risk factors, and diabetes status.

§Adjusted for age, sex, obesity, diabetes mellitus, hypertension, hyperlipidemia, current smoking, family history of coronary artery disease, and high-sensitivity C-reactive protein ≥2 mg/L.

¶Adjusted for age, gender, body mass index, regular exercise and current smoking waist circumference, triglycerides, low-density lipoprotein cholesterol, diabetes mellitus, and hypertension.

‖Adjusted for type 2 diabetes, systolic blood pressure, total cholesterol level, statin use, and hypertension.

#Multivariate Cox regression analysis.

**Adjusted for age, gender, smoking, hyperlipidemia, hypertension, diabetes, and smoking.

††Adjusted for age, sex, obesity, hypertension, dyslipidemia, diabetes, smoking history, antiplatelet agents, lipid-lowering agents, and family history of heart disease in the first-degree relatives.

‡‡Adjusted for age, sex, current smoking, regular exercise, income, body weight, total cholesterol, hypertension, diabetes, and use of medication for dyslipidemia.

§§Cohorts were matched based on age, sex, treating physician, type 2 diabetes, arterial hypertension, and hyperlipidemia.

¶¶Adjusted for age, sex, and year of visit.

‖‖Adjusted age, sex, smoking, hypertension, diabetes mellitus, low-density lipoprotein cholesterol, and waist circumference.

##Adjusted for age, gender, body mass index, obese, smoking, metabolic syndrome, hypertension, diabetes, alanine aminotransferase, serum total cholesterol, triglyceride, and low-density lipoprotein cholesterol.

***Adjusted for age, sex, physical activity, body mass index, smoker, history of hypertension, diabetes, atrial fibrillation and hypercholesterolemia, lipid-lowering medication, high-density lipoprotein, triglyceride, and high-sensitivity C-reactive protein, fasting blood glucose.

†††Adjusted for age, sex, race, assessment center, smoking, Townsend index, systolic blood pressure, diastolic blood pressure, non–high-density lipoprotein cholesterol, antihypertensive treatment, lipid-lowering treatment, HbA1c, and antidiabetic treatment.

0.96–1.00). The OR for IHD per M-allele higher genetically determined liver fat content was 0.98 (95% CI, 0.94–1.03).[36] There were a few limitations of this study, including liver fat content measurements were only available for a small proportion of subjects, ethnic differences, lower body mass index (BMI), and only 1 functional variant as a genetic instrument for liver fat. Regardless, it is conceivable that these genetic variants may serve as important biomarkers to assess the risk of ASCVD in patients with NAFLD in the future.

POTENTIAL PROATHEROGENIC MECHANISMS OF NAFLD

Although the exact proatherogenic mechanism of NAFLD has not been completely elucidated, numerous studies have offered possible explanations of the underlying mechanisms that govern the complex interplay between liver and cardiovascular system. Possible direct mechanisms such as insulin resistance (IR), dyslipidemia, systemic inflammation, and oxidative stress driven by NAFLD have been demonstrated to promote endothelial cell damage, inflammatory cell activation, foam cell formation, and smooth muscle cell proliferation in the arteries, eventually leading to atherosclerosis. The presence of diabetes and MetS may also confound the pathophysiological relationship between NAFLD and atherosclerosis, because of the shared overlapping risk factors. The intricate link between NAFLD and atherosclerosis is illustrated in Figure 1.

Direct Contributors to the Proatherogenic Mechanism of CVD

IR, a hallmark of NAFLD characterized by reduced insulin sensitivity not just in the liver, but also skeletal muscles and adipose tissue, promotes atherosclerosis.[37] IR can be involved in many dysmetabolic processes such as lipid metabolism, glucose metabolism, activating oxidative stress, and inflammation, creating a proatherogenic environment predisposing to atherosclerosis.[37] As a result of IR, adipose tissue undergoes lipolysis, leading to the breakdown of triglycerides stored in fat cells, releasing free fatty acids.[37] These free fatty acids are transported to the liver where they stabilize the production of apolipoprotein B, which is a structural protein that constitutes a major component of very-low-density lipoprotein (VLDL).[38] Reduced insulin signaling

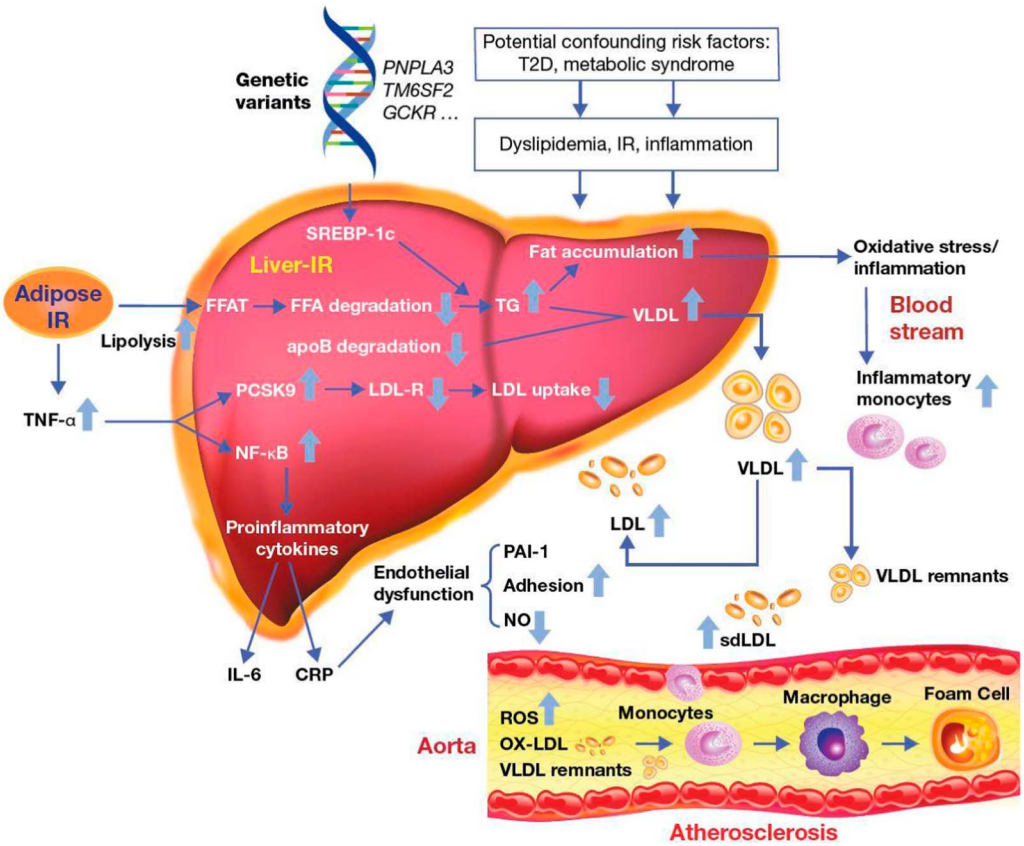

FIGURE 1. Potential proatherogenic mechanisms of NAFLD. ApoB, apolipoprotein B; FFA, free fatty acid; CRP, C-reactive protein; IL-6, interleukin-6; IKK-β, IκB kinase; IR, insulin resistance; LDL-C, low-density lipoprotein cholesterol; LDL-R, low-density lipoprotein-receptor; NF-κB, nuclear factor-kappa B; NO, nitric oxide; OX-LDL, oxidized low-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; PCSK9, proprotein convertase subtilisin/kexin type 9; ROS, reactive oxygen species; sdLDL, small dense low-density lipoprotein; LDL-R, low-density lipoprotein-receptor; SREBP-1c, sterol regulatory element-binding protein 1-c; TG, triglyceride; TNF-α, tumor necrosis factor-α; T2D, type 2 diabetes; VLDL, very-low-density lipoprotein.

because of IR further prevents the degradation of apolipoprotein B, which in turn increases VLDL production in the hepatocytes.[39] VLDL is secreted from the liver into the bloodstream, and its remnants quickly penetrate the arterial wall, inducing endothelial dysfunction and the uptake of inflammatory monocytes, which eventually results in the accumulation of foam cells.[38] A key underlying feature of other metabolic disorders such as type 2 diabetes mellitus (T2DM) and MetS is IR. IR, in turn, is a common pathophysiological mechanism shared by the 2 aforementioned conditions and NAFLD. Therefore, IR could be considered a fundamental contributor to ASCVD as it is associated with impaired glucose tolerance, visceral adiposity, obesity, metabolic syndrome, and T2DM—all of which are related to excess risk of NAFLD.

Atherogenic dyslipidemia is characterized by elevated levels of triglycerides, small-dense LDL, and low levels of high-density lipoprotein cholesterol (HDL-C).[38] The liver is involved in the metabolism of lipoproteins, and this metabolic process is disrupted in NAFLD patients, leading to the upregulation of the sterol regulatory element binding protein-1c (SREBP-1c). SREBP-1c is known to regulate de novo lipogenesis and metabolism of triglyceride-rich lipoprotein.[40] de novo lipogenesis drives NAFLD by promoting liver fat accumulation through increased triglyceride synthesis and reducing breakdown of fatty acids, further disturbing the atherogenic lipid profile.[40] Other than aberrant lipoprotein metabolism, small-dense LDL derived from the proatherogenic VLDL1—a subclass of VLDL with higher triglyceride content—can easily infiltrate the arterial wall and promote the development of atherosclerotic plaques in NAFLD patients.[38]

Inflammation is also a principal feature of NAFLD.[41] Fat accumulation in the liver and oxidative stress can also induce the secretions of inflammatory cytokines. Increased systemic inflammation has been detected in patients with NAFLD, including elevated levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6, and high-sensitivity C-reactive protein (hs-CRP), among others.[41] These proinflammatory cytokines that are released to circulation are believed to have a direct implication on atherosclerotic progress. TNF-α plays a pivotal role in mediating inflammation. Large amount of TNF-α is secreted into the bloodstream by IR-abdominal adipose tissues.[42] This in turn activates hepatic production of TNF-α, which upregulates key molecules associated with lipid metabolism, inflammatory cytokines, and fibrosis in the liver.[42] High levels of TNF-α are associated with increased risk of coronary events. Other than being upregulated by inflammatory mediators, genetic variations in TNF-α can alter protein expression, contributing to the risk of CVD. In 1 study, the presence of TNF-α polymorphisms at residues 238 and 308 in patients with NAFLD showed an increased risk of developing CAD.[43] Exposure of hepatocytes to TNF-α was previously reported to induce the expression of PCSK9, a protein which is involved in lipid metabolism.[44] PCSK9 secreted by the liver cells inhibits LDL uptake by degrading LDL-receptor. In 1 study, circulating PCSK9 correlated positively to the severity of hepatic steatosis.[45] Hence, it is plausible that TNF-α induces PCSK9, which in turn disrupts LDL metabolism, contributing to elevated LDL-C levels commonly observed in atherosclerosis. Given that treatments targeting PCSK9 significantly reduce cardiovascular mortality and that data suggest circulating PCSK9 is involved in vascular damage, altered secretion of PCSK9 in individuals with NAFLD may be involved in the pathogenesis of atherosclerosis.[45] High circulating concentrations of IL-6 are associated with CVD, including endothelial dysfunction, stiffness of the arteries, and atherosclerosis.[46] In addition, IL-6 is the primary hepatic stimulant for CRP synthesis. CRP produced mainly in the liver is believed to actively contribute to atherosclerosis by increasing the expression of plasminogen activator inhibitor-1 (PAI-1) and adhesion molecules in endothelial cells, inhibiting nitric oxide formation, and increasing LDL uptake by macrophages.[37,47] High circulating levels of PAI-1 have been detected in patients with NAFLD.[46] Elevated PAI-1 concentration has a direct effect on atherothrombosis by activating the coagulation cascade via reducing fibrinolytic activity.[48]

Oxidative stress caused by fat accumulation in the liver, persistent IR, and hyperglycemia has been reported to play a role in increasing CVD risk in patients with NAFLD, indicating a shared pathophysiological condition between both disorders. Oxidative stress is a result of imbalance between the production of reactive oxygen species (ROS) and dysfunction in the antioxidant system.[49] In the liver, ROS contributes to the upregulation of proinflammatory cytokines, apoptosis, and fibrosis, aggravating oxidative stress and resulting in a vicious cycle.[49] Excessive production of ROS disrupts endothelial function resulting in the formation and deposition of oxidized LDL in the subendothelial space.[50] ROS may also promote the transformation of macrophages into foam cells through the oxidation of LDL, 1 of the key steps in the formation of atherosclerotic lesion,[50] and cause lipid to degrade predisposing to inflammation, adding further atherogenic stimuli to the already highly oxidative and proinflammatory environment. Taken together, the proinflammatory environment liberated by the liver could trigger plaque formation, change in vascular tone, disrupting endothelial function, potentially contributing to the atherosclerotic process.

Indirect Contributors to the Proatherogenic Mechanism of CVD

Traditional risk factors for ASCVD, such as T2DM and MetS, are also risk factors for NAFLD, these present confounding contributors to atherosclerotic cardiovascular events in NAFLD patients.[51] Moreover, individuals with NAFLD are at an increased risk of developing diabetes and MetS, both of which are established risk factors of ASCVD. There is evidence suggesting that NAFLD is associated with increased risk of ASCVD among patients with T2DM. In 1 meta-analysis comparing T2DM patients with and without NAFLD, a synergistic elevation of cardiovascular risk with the presence of T2DM and NAFLD has been reported.[52] Similarly, patients with NAFLD had a higher risk of cardiovascular events compared with those without, independently of MetS, and the risk is further elevated with the presence of liver fibrosis.[8] These studies show that among individuals

with the same ASCVD traditional risk factors, the risk of atherosclerotic events is greater in the presence of NAFLD, indicating that NAFLD may confer an excess ASCVD risk beyond the underlying metabolic disorders.

NAFLD AS A POTENTIAL TREATMENT TARGET FOR ASCVD

Evidence-Based Guidelines and Expert Recommendations

Patients with NAFLD are at risk of cardiovascular morbidity and mortality; therefore, CVD risk factors should be aggressively mitigated along with the management of the liver disease itself.[2–4] In the Chinese guidelines, patients with NAFLD should be assessed regularly and monitored for the risk and complication of ASCVD.[2] Lifestyle modifications such as dietary changes, weight loss, and reduction of waist circumference are recommended to prevent and treat NAFLD by reducing cardiovascular risk factors.[2–4] Pharmacotherapy can be considered in those with NAFLD who have failed to control their metabolic risk factors. Renin–angiotensin system inhibitors are known to improve IR, alleviate arterial hypertension, and are safe for use in patients with NAFLD; omega-3 polyunsaturated fatty acid may reduce liver fat accumulation and help manage triglyceride-rich lipoprotein—a risk factor of atherosclerosis—in NAFLD; glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been proven to reduce cardiovascular deaths and resolve NAFLD; and statins can be used to reduce LDL-C and prevent cardiovascular risk with good liver safety except in patients with liver failure and decompensated cirrhosis.[2–4] Other agents that could reduce cardiovascular risk factors in patients with NAFLD include metformin and pioglitazone. The former could be used to control IR without any adverse effect on the liver whereas the latter should be considered in NAFLD patients with T2DM who are potentially at higher risk of cardiovascular events.[2–4]

ASCVD Risk Stratification According to NAFLD Severity

NAFLD frequently accompanies other metabolic abnormalities. The presence of concomitant conditions could potentially deliver an additive effect, accelerating atherosclerotic progression. Studies have shown that patients with NAFLD and MetS were at higher risk of atherosclerotic progression.[9,51] Higher fatty liver index or severity of NAFLD has also been associated with increased risk of cardiovascular events such as MI and IS.[18,20,21] Higher incidences of T2DM have also been associated with increasing NAFLD severity.[51,52] Screening for NAFLD with standardized diagnostic tools and assessing the severity[2,4] could estimate the risk of ASCVD; this in turn could inform the potential benefits of earlier preventive and treatment strategies. Several international guidelines strongly recommend patients with NAFLD be screened or regularly assessed for other metabolic syndromes and risk factors of cardiovascular complications.[2,4] In routine clinical care, management of ASCVD in patients with NAFLD should be guided by risk stratification.

LIFESTYLE MODIFICATION

Lifestyle modifications such as weight loss, dietary control, and increased physical activity are the mainstay of NAFLD management.[2–4] The aim is to improve insulin sensitivity and reduce visceral obesity, thereby lowering the risk of extrahepatic complications such as ASCVD. Body-weight loss of at least 3–5% can improve hepatic steatosis; ≥7% to reduce serum levels of transaminases and NASH; and at least 10% to reverse liver fibrosis.[2–4] Weight-lowering medications may be appropriate and effective at achieving sustained weight loss especially in obese patients; however, the adverse effects of these medications should be monitored, and long-term use avoided.[2] Adherence to long-term moderate aerobic exercise and/or resistance training can reduce liver fat effectively.[2,4] Physical activity also has a positive effect on the shared risk factors of NAFLD and ASCVD such as IR, elevated triglycerides, obesity, and low high-density lipoprotein cholesterol levels.[53] Regarding diet, guidelines recommend restricting calorie intake by 500–1000 kcal to induce weight loss of 0.5–1.0 kg/wk.[2–4] Excessive alcohol consumption should be avoided to reduce further accelerating liver fibrosis or acute liver injury,[2–4] whereas light alcohol consumption suggests a beneficial effect on NAFLD.[3,4]

THERAPEUTIC APPROACHES TO REDUCING ASCVD RISK IN PATIENTS WITH NAFLD

Lipid-Lowering Agents

Statins serve as cholesterol-lowering drugs that are proven to reduce ASCVD risk. Because patients with NAFLD and NASH have a higher incidence of atherosclerotic complications, individuals with this liver disorder should benefit from statins. The Chinese Guidelines of prevention and treatment of nonalcoholic fatty liver disease and European Association for the Study of the Liver stated that the use of statins is safe for patients with NAFLD and NASH to lower LDL-C and prevent cardiovascular events.[2,4] Although, to date, there are no randomized controlled trials to evaluate the specific role of statins on NASH and liver fibrosis. There are 2 *post hoc* analyses of large prospective randomized clinical trials that demonstrated the effect of statins on NASH, the IDEAL and GREACE studies observed that statins treatment significantly improved NAFLD and cardiovascular outcomes in patients with elevated transaminases.[54,55] Therefore, statins are likely to exhibit cardiologic and hepatologic protection, even though there is a mild risk of elevated hepatic transaminase elevations.[2–5]

Xuezhikang (XZK), an extract of red yeast rice, is mainly used in traditional Chinese medicine, and is regarded as a natural lipid-lowering medicine to treat ASCVD and also has a positive effect on the liver.[56,57] In a multicenter study, patients with dyslipidemia who received XZK were able to achieve a 27% reduction in LDL-C compared with placebo, other atherogenic lipoproteins were also significantly reduced in patients with dyslipidemia.[57] A *post hoc* analysis of the Chinese Coronary Secondary Prevention Study—a large randomized controlled trial designed to compare the effect of XZK in reducing cardiovascular events with placebo—was

conducted in 820 patients with mild-to-moderate abnormal liver tests, defined as serum alanine aminotransferase concentration of less than 3 times the upper limit of normal. During 4.5 years of follow-up, XZK improved lipid and liver profiles of patients with abnormal liver tests; interestingly, XZK-related risk reduction of major coronary events was higher in patients with abnormal liver tests ($n = 401$) than those with normal liver tests ($n = 1781$) (76.3% vs. 40.1%, $P = 0.009$).[56] These data provide evidence for the clinical benefit and long-term safety of XZK in abnormal liver conditions.

PCSK9 has been involved in the complex interplay of NAFLD and atherosclerosis, and PCSK9 inhibitors are a relatively new class of lipid-lowering drug that exhibits excellent potency to lower LDL-C with proven efficacy in reducing cardiovascular events. Recently, PCSK9 inhibitors have emerged as potential therapeutic agents to ameliorate NAFLD by inhibiting lipid accumulation in the liver.[58] In a retrospective study, 29 patients who had received PCSK9 inhibitors were analyzed to determine whether the lipid-lowering drug could improve fatty infiltration of the liver.[59] These patients were treated with PCSK9 inhibitors for a mean duration of 23.7 months and experienced improvement in serum alanine aminotransferase and aspartate aminotransferase levels. Of the 11 who were diagnosed with hepatic steatosis, 8 of them achieved complete resolution after the use of PCSK9 inhibitors.[59] In another study, the use of berberine, a naturally occurring lipid-lowering plant-based compound with known effects on PCSK9 reduction, was able to reduce hepatic fat content and improve lipid profile.[60] Larger randomized controlled studies are needed to confirm the cardiovascular and liver beneficial effects of PCSK9 inhibitors on NAFLD/NASH.

New Glucose-Lowering Agents

GLP-1 RAs exhibit hypoglycemic effects that can significantly reduce body weight with CVD benefits. Studies have shown that GLP-1 RAs may modestly improve NAFLD and reduced risk of major adverse cardiovascular event. In the phase IIb LEAN trial, 52 obese patients with NASH who received liraglutide 1.8 mg daily had significantly higher rates of NASH resolution over 48 weeks compared with controls.[61] Liraglutide has also shown reduction in C-IMT in patients with T2DM and NAFLD.[62] Semaglutide is another GLP-1 RA that improved NAFLD/NASH reducing inflammatory cytokines production in the liver and attenuated atherosclerotic lesions in atherosclerosis-susceptible mouse models.[63] More recently, treatment with semaglutide showed that most patients were likely to have resolution of NASH without worsening of fibrosis versus placebo in a dose-dependent manner.[64] Although the therapeutic mechanisms of GLP-1 RA on NALFD are still not precisely known, studies have shown that GLP-1 RAs improve key parameters involved in NAFLD through an incretin effect and directly reduce the lipid metabolism of hepatocytes and inflammation in liver, thereby reversing the progression of NAFLD and reducing ASCVD risk.[5,61,63] Additional studies are warranted to provide valuable mechanistic insight into how GLP-1 RAs are able to provide cardiovascular benefit through NAFLD or NASH resolution.

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors prevent renal tubule glucose reabsorption thereby lowering blood glucose levels, resulting in significant weight loss. The SGLT-2 inhibitors induce a variety of beneficial effects that attenuate the development of cardiomyopathy.[65,66] In a meta-analysis of randomized controlled trials by Wei et al, SGLT-2 inhibitors improved liver enzymes, reduced liver fat and body weight, thereby improving liver fibrosis in patients with NAFLD and T2DM.[65] These results were further verified in another recent meta-analysis of 1498 patients with NAFLD, demonstrating that SGLT-2 inhibitors improved BMI, glucose metabolism, lipid metabolism, liver function, and liver fibrosis.[67] In a preclinical study using atherosclerotic mouse models, treatment with the SGLT-2 inhibitor empagliflozin for 5 weeks attenuated NAFLD progression by promoting autophagy, reducing ER stress, and inhibiting hepatic apoptosis in atherosclerosis-susceptible mice.[66] These studies add to the mechanistic evidence on the beneficial effect of SGLT-2 inhibitors on NAFLD and ASCVD.

Drug Development in NAFLD

To date, there are a considerable number of drugs at various stages of development that target different pathways of NAFLD. Although most of them focus on the histological improvement of the liver, cardiovascular endpoints also deserve more attention, given that cardiovascular death accounts for a significant proportion of extrahepatic mortality in NAFLD.

CONCLUSION

The increased global prevalence of NAFLD in recent years has brought more attention to its associated risk for ASCVD. However, this has not been widely recognized clinically. Although the debate remains regarding a causal relationship between NAFLD and ASCVD, numerous genetic, epidemiologic, and observational studies support that NAFLD may serve as an emerging risk factor for ASCVD. Meanwhile, the multiple proatherogenic mechanisms of NAFLD have been illustrated and reasonably demonstrated a strong association between both disorders. Recent guidelines on cardiovascular and liver diseases recommend stratifying the future risk of ASCVD in NAFLD patients and controlling their associated risk factors to reduce the complications that could potentially arise from both disorders. As of now, many therapeutic interventions are still under development owing to the complexity and heterogeneity in the pathogenesis of NAFLD. Lipid-lowering agents, including statins, traditional XZK, and new PCSK9 inhibitors, have provided the evidence for liver safety and protection in reducing ASCVD risk. New glucose-lowering drugs such as SGLT-2 inhibitors and GLP-1 RAs have exhibited potential benefit to both the liver histological resolution of NAFLD and the risk reduction on cardiovascular events. More studies are needed to understand the underlying pathophysiological pathways and biochemical markers that are responsible for the association of NAFLD and ASCVD. Importantly, clinical trials of new drug development for NAFLD should also simultaneously evaluate CVD outcomes.

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REFERENCES

1. Li J, Zou B, Yeo YH, et al. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999-2019: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2019;4:389–398.
2. Fan JG, Wei L, Zhuang H, et al. Guidelines of prevention and treatment of nonalcoholic fatty liver disease (2018, China). *J Dig Dis.* 2019;20: 163–173.
3. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. *Hepatology*. 2018;67:328–357.
4. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD). European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol.* 2016;64:1388–1402.
5. Duell PB, Welty FK, Miller M, et al. Nonalcoholic fatty liver disease and cardiovascular risk: a scientific statement from the American heart association. *Arteriosclerosis, Thromb Vasc Biol.* 2022;42:e168–e185.
6. Ghoneim S, Dhorepatil A, Shah AR, et al. Non-alcoholic steatohepatitis and the risk of myocardial infarction: a population-based national study. *World J Hepatol.* 2020;12:378–388.
7. Labenz C, Huber Y, Michel M, et al. Impact of NAFLD on the incidence of cardiovascular diseases in a primary care population in Germany. *Dig Dis Sci.* 2020;65:2112–2119.
8. Baratta F, Pastori D, Angelico F, et al. Nonalcoholic fatty liver disease and fibrosis associated with increased risk of cardiovascular events in a prospective study. *Clin Gastroenterol Hepatol.* 2020;18: 2324–2331.e4.
9. Cho YK, Kang YM, Yoo JH, et al. The impact of non-alcoholic fatty liver disease and metabolic syndrome on the progression of coronary artery calcification. *Sci Rep.* 2018;8:12004.
10. Gummesson A, Stromberg U, Schmidt C, et al. Non-alcoholic fatty liver disease is a strong predictor of coronary artery calcification in metabolically healthy subjects: a cross-sectional, population-based study in middle-aged subjects. *PLoS One*. 2018;13:e0202666.
11. Hsu PF, Wang YW, Lin CC, et al. The association of the steatosis severity in fatty liver disease with coronary plaque pattern in general population. *Liver Int*. 2021;41:81–90.
12. Koo BK, Allison MA, Criqui MH, et al. The association between liver fat and systemic calcified atherosclerosis. *J Vasc Surg.* 2020;71:204–211.e4.
13. Lee SB, Park GM, Lee JY, et al. Association between non-alcoholic fatty liver disease and subclinical coronary atherosclerosis: an observational cohort study. *J Hepatol.* 2018;68:1018–1024.
14. Sinn DH, Kang D, Chang Y, et al. Non-alcoholic fatty liver disease and progression of coronary artery calcium score: a retrospective cohort study. *Gut*. 2017;66:323–329.
15. Tang K, Lin J, Ji X, et al. Non-alcoholic fatty liver disease with reduced myocardial FDG uptake is associated with coronary atherosclerosis. *J Nucl Cardiol.* 2021;28:610–620.
16. Zheng J, Zhou Y, Zhang K, et al. Association between nonalcoholic fatty liver disease and subclinical atherosclerosis: a cross-sectional study on population over 40 years old. *BMC Cardiovasc Disord.* 2018;18:147.
17. Alexander M, Loomis AK, van der Lei J, et al. Non-alcoholic fatty liver disease and risk of incident acute myocardial infarction and stroke: findings from matched cohort study of 18 million European adults. *BMJ*. 2019;367:l5367.
18. Kim JH, Moon JS, Byun SJ, et al. Fatty liver index and development of cardiovascular disease in Koreans without pre-existing myocardial infarction and ischemic stroke: a large population-based study. *Cardiovasc Diabetol.* 2020;19:51.
19. Sinn DH, Kang D, Chang Y, et al. Non-alcoholic fatty liver disease and the incidence of myocardial infarction: a cohort study. *J Gastroenterol Hepatol.* 2020;35:833–839.
20. Xu J, Dai L, Zhang Y, et al. Severity of nonalcoholic fatty liver disease and risk of future ischemic stroke events. *Stroke*. 2021;52:103–110.
21. Zou B, Yeo YH, Cheung R, et al. Fatty liver index and development of cardiovascular disease: findings from the UK Biobank. *Dig Dis Sci.* 2021;66:2092–2100.
22. Koulaouzidis G, Charisopoulou D, Kukla M, et al. Association of non-alcoholic fatty liver disease with coronary artery calcification progression: a systematic review and meta-analysis. *Prz Gastroenterol.* 2021;16: 196–206.
23. Wong MYZ, Yap JJL, Sultana R, et al. Association between non-alcoholic fatty liver disease and subclinical atherosclerosis in Western and Asian cohorts: an updated meta-analysis. *Open Heart*. 2021;8: e001850.
24. Estes C, Anstee QM, Arias-Loste MT, et al. Modeling NAFLD disease burden in China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States for the period 2016-2030. *J Hepatol.* 2018;69:896–904.
25. Adams LA, Lymp JF, St Sauver J, et al. The natural history of non-alcoholic fatty liver disease: a population-based cohort study. *Gastroenterology*. 2005;129:113–121.
26. Pisto P, Santaniemi M, Bloigu R, et al. Fatty liver predicts the risk for cardiovascular events in middle-aged population: a population-based cohort study. *BMJ Open*. 2014;4:e004973.
27. Zhou F, Zhou J, Wang W, et al. Unexpected rapid increase in the burden of NAFLD in China from 2008 to 2018: a systematic review and meta-analysis. *Hepatology*. 2019;70:1119–1133.
28. Targher G, Byrne CD, Lonardo A, et al. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: a meta-analysis. *J Hepatol.* 2016;65:589–600.
29. Petta S, Valenti L, Marchesini G, et al. PNPLA3 GG genotype and carotid atherosclerosis in patients with non-alcoholic fatty liver disease. *PLoS One*. 2013;8:e74089.
30. Xia MF, Ling Y, Bian H, et al. I148M variant of PNPLA3 increases the susceptibility to non-alcoholic fatty liver disease caused by obesity and metabolic disorders. *Aliment Pharmacol Ther.* 2016;43:631–642.
31. Dongiovanni P, Petta S, Maglio C, et al. Transmembrane 6 superfamily member 2 gene variant disentangles nonalcoholic steatohepatitis from cardiovascular disease. *Hepatology*. 2015;61:506–514.
32. Wu JT, Liu SS, Xie XJ, et al. Independent and joint correlation of PNPLA3 I148M and TM6SF2 E167K variants with the risk of coronary heart disease in patients with non-alcoholic fatty liver disease. *Lipids Health Dis*. 2020;19:29.
33. Gao H, Liu S, Zhao Z, et al. Association of GCKR gene polymorphisms with the risk of nonalcoholic fatty liver disease and coronary artery disease in a Chinese Northern Han Population. *J Clin Translational Hepatol.* 2019;X:1–7.
34. Castaldo L, Laguzzi F, Strawbridge RJ, et al. Genetic variants associated with non-alcoholic fatty liver disease do not associate with measures of sub-clinical atherosclerosis: results from the IMPROVE study. *Genes (Basel)*. 2020;11:1243.
35. Liu DJ, Peloso GM, Yu H, et al. Exome-wide association study of plasma lipids in >300,000 individuals. *Nat Genet.* 2017;49:1758–1766.
36. Lauridsen BK, Stender S, Kristensen TS, et al. Liver fat content, non-alcoholic fatty liver disease, and ischaemic heart disease: mendelian randomization and meta-analysis of 279 013 individuals. *Eur Heart J.* 2018;39:385–393.
37. Gaggini M, Morelli M, Buzzigoli E, et al. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. *Nutrients*. 2013;5:1544–1560.
38. Deprince A, Haas JT, Staels B. Dysregulated lipid metabolism links NAFLD to cardiovascular disease. *Mol Metab.* 2020;42:101092.
39. Haas ME, Attie AD, Biddinger SB. The regulation of ApoB metabolism by insulin. *Trends Endocrinol Metab.* 2013;24:391–397.
40. Xu X, Lu L, Dong Q, et al. Research advances in the relationship between nonalcoholic fatty liver disease and atherosclerosis. *Lipids Health Dis*. 2015;14:158.

41. Haukeland JW, Damas JK, Konopski Z, et al. Systemic inflammation in nonalcoholic fatty liver disease is characterized by elevated levels of CCL2. *J Hepatol.* 2006;44:1167–1174.
42. Stojsavljevic S, Gomercic Palcic M, Virovic Jukic L, et al. Adipokines and proinflammatory cytokines, the key mediators in the pathogenesis of nonalcoholic fatty liver disease. *World J Gastroenterol.* 2014;20:18070–18091.
43. Cheng Y, An B, Jiang M, et al. Association of tumor necrosis factor-alpha polymorphisms and risk of coronary artery disease in patients with non-alcoholic fatty liver disease. *Hepat Mon.* 2015;15:e26818.
44. Ruscica M, Ricci C, Macchi C, et al. Suppressor of cytokine signaling-3 (SOCS-3) induces proprotein convertase subtilisin kexin type 9 (PCSK9) expression in hepatic HepG2 cell line. *J Biol Chem.* 2016;291:3508–3519.
45. Ruscica M, Ferri N, Macchi C, et al. Liver fat accumulation is associated with circulating PCSK9. *Ann Med.* 2016;48:384–391.
46. Simon TG, Trejo MEP, McClelland R, et al. Circulating Interleukin-6 is a biomarker for coronary atherosclerosis in nonalcoholic fatty liver disease: results from the Multi-Ethnic Study of Atherosclerosis. *Int J Cardiol.* 2018;259:198–204.
47. Badimon L, Pena E, Arderiu G, et al. C-reactive protein in atherothrombosis and angiogenesis. *Front Immunol*. 2018;9:430.
48. Alessi MC, Bastelica D, Mavri A, et al. Plasma PAI-1 levels are more strongly related to liver steatosis than to adipose tissue accumulation. *Arteriosclerosis, Thromb Vasc Biol.* 2003;23:1262–1268.
49. Ferro D, Baratta F, Pastori D, et al. New insights into the pathogenesis of non-alcoholic fatty liver disease: gut-derived Lipopolysaccharides and oxidative stress. *Nutrients*. 2020;12:2762.
50. Polimeni L, Del Ben M, Baratta F, et al. Oxidative stress: new insights on the association of non-alcoholic fatty liver disease and atherosclerosis. *World J Hepatol.* 2015;7:1325–1336.
51. Lee HH, Cho Y, Choi YJ, et al. Non-alcoholic steatohepatitis and progression of carotid atherosclerosis in patients with type 2 diabetes: a Korean cohort study. *Cardiovasc Diabetol.* 2020;19:81.
52. Zhou YY, Zhou XD, Wu SJ, et al. Synergistic increase in cardiovascular risk in diabetes mellitus with nonalcoholic fatty liver disease: a meta-analysis. *Eur J Gastroenterol Hepatol.* 2018;30:631–636.
53. Kwak MS, Kim D. Non-alcoholic fatty liver disease and lifestyle modifications, focusing on physical activity. *Korean J Intern Med*. 2018;33:64–74.
54. Tikkanen MJ, Fayyad R, Faergeman O, et al. Effect of intensive lipid lowering with atorvastatin on cardiovascular outcomes in coronary heart disease patients with mild-to-moderate baseline elevations in alanine aminotransferase levels. *Int J Cardiol.* 2013;168:3846–3852.
55. Athyros VG, Tziomalos K, Gossios TD, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. *Lancet*. 2010;376:1916–1922.
56. Li JJ, Lu ZL, Kou WR, et al. Impact of long-term xuezhikang therapy on cardiovascular events in high-risk patients with nonspecific, preexisting abnormal liver tests: a post-hoc analysis from Chinese Coronary Secondary Prevention Study (CCSPS). *Int J Cardiol.* 2012;154:362–365. doi.
57. Moriarty PM, Roth EM, Karns A, et al. Effects of xuezhikang in patients with dyslipidemia: a multicenter, randomized, placebo-controlled study. *J Clin Lipidol.* 2014;8:568–575.
58. Theocharidou E, Papademetriou M, Reklou A, et al. The role of PCSK9 in the pathogenesis of non-alcoholic fatty liver disease and the effect of PCSK9 inhibitors. *Curr Pharm Des.* 2019;24:3654–3657.
59. Shafiq M, Walmann T, Nutalapati V, et al. Effects of proprotein convertase subtilisin/kexin type-9 inhibitors on fatty liver. *World J Hepatol.* 2020;12:1258–1266.
60. Yan HM, Xia MF, Wang Y, et al. Efficacy of berberine in patients with non-alcoholic fatty liver disease. *PLoS One*. 2015;10:e0134172.
61. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet*. 2016;387:679–690.
62. Rizvi AA, Patti AM, Giglio RV, et al. Liraglutide improves carotid intima-media thickness in patients with type 2 diabetes and non-alcoholic fatty liver disease: an 8-month prospective pilot study. *Expert Opin Biol Ther.* 2015;15:1391–1397.
63. Rakipovski G, Rolin B, Nohr J, et al. The GLP-1 Analogs liraglutide and semaglutide reduce atherosclerosis in $ApoE^{-/-}$ and $LDLr^{-/-}$ mice by a mechanism that includes inflammatory pathways. *JACC: Basic Translational Sci.* 2018;3:844–857.
64. Newsome PN, Buchholtz K, Cusi K, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. *N Engl J Med.* 2021;384:1113–1124.
65. Wei Q, Xu X, Guo L, et al. Effect of SGLT2 inhibitors on type 2 diabetes mellitus with non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials. *Front Endocrinol (Lausanne)*. 2021;12:635556.
66. Nasiri-Ansari N, Nikolopoulou C, Papoutsi K, et al. Empagliflozin attenuates non-alcoholic fatty liver disease (NAFLD) in high fat diet fed $ApoE^{(-/-)}$ mice by activating autophagy and reducing ER stress and apoptosis. *Int J Mol Sci.* 2021;22:818.
67. Mo M, Huang Z, Liang Y, et al. The safety and efficacy evaluation of sodium-glucose co-transporter 2 inhibitors for patients with non-alcoholic fatty liver disease: an updated meta-analysis. *Dig Liver Dis.* 2022;54:461-468.